DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Central Region

Food and Drug Administration
Waterview Corporate Center
10 Waterview Blvd., 3rd Floor
Parsippany, NJ 07054

Telephone (973) 526-6006

October 22, 2003

CERTIFIED MAIL –
RETURN RECEIPT REQUESTED

WARNING LETTER

Dr. Albert H. Ahn
Corporate Vice President & Chief Scientific Officer
Hartz Mountain Corporation
400 Plaza Drive
Secaucus, New Jersey 07094-3688 04-NWJ-04

Dear Dr. Ahn:

During the inspections of your veterinary drug manufacturing facility, Hartz Mountain Corporation, located at 192 Bloomfield Avenue, Bloomfield, N.J. between February 25, 2003-March 5, 2003 and May 28, 2003 – June 30, 2003, investigators from the Food and Drug Administration (FDA) documented significant deviations from Current Good Manufacturing Practices (CGMP's) for Finished Pharmaceuticals (Code of Federal Regulations), Title 21, Parts 210 and 211. These finished pharmaceutical deviations causes your Hydrocortisone (Anti-Itch Spot, Spray, Shampoo) and Once-a-Month Wormer capsules to be adulterated within the meaning of Section 501(a)(2)(B), and misbranded within the meaning of Section 502(f)(2), of the Federal Food, Drug and Cosmetic Act (The Act). The above referenced products are drugs within the meaning of section 201(g) of The Act.

Current Good Manufacturing Practice (CGMP) regulations (21 CFR Parts 210 & 211) pertain to the production of all drug products regardless of whether they are intended for administration to humans or animals. The inspections revealed the following significant deficiencies:

1. Contrary to the requirements of 21 CFR Part 211.67, your firm has not demonstrated that the cleaning procedures provided in your Hydrocortisone spray and shampoo batch records can remove pesticide residuals and detergent residues from non-dedicated manufacturing equipment. There is no assurance of the effectiveness of your cleaning procedures to remove insecticide residue and detergent residue after flushing with deionized water to prevent product contamination of the following Hydrocortisone (Spray and Shampoo) lots:

Lot # BL09431 (Control Flea & Tick Repellent) containing [redacted] insecticide was manufactured in [redacted] on [redacted] prior to the manufacture of lot # BL10531 (Hydrocortisone Spray) on [redacted]

Lot # BL10031 (Flea & Tick Conditioning Shampoo) containing [redacted] insecticide was in [redacted] prior to lot # BL10531 (Hydrocortisone Spray) on [redacted]

Lot # BL00231 (Rid Flea Shampoo) containing [redacted] insecticide was manufactured in [redacted] on [redacted] prior to lot # BL08431 (Hydrocortisone Shampoo) on [redacted]

Lot # BL09231 (Control IGR Dog/Cat Repellent) containing [redacted] and [redacted] was in [redacted] on [redacted] prior to lot # BL08431 (Hydrocortisone Shampoo) on [redacted]

2. Written procedures for production and process controls do not assure that drug products have the identity, strength, quality, and purity they purport or are represented to possess as required by 21 CFR 211.100(a). Specifically, process validation studies have not been completed for the manufacturing of Hydrocortisone Anti-itch Spot (lot # BL11431 which was released on [redacted] Hydrocortisone Shampoo (lot # BL08431 which was released on [redacted], and Hydrocortisone Spray (lot # BL10731 which was released on [redacted]

3. Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product as required by 21 CFR 211.110(a). For example:

   A) The manufacturing batch record for lot # BL08431 (Hydrocortisone Shampoo) documented a mixing time of [redacted] minutes ([redacted] for the [redacted] where batch record lot # BL11231 (Hydrocortisone Shampoo) documented a [redacted] minute mix time for the same steps. In addition, batch record BL08431 documented a mixing time of [redacted] minutes ([redacted] for [redacted] where batch record BL11231documented a [redacted] minute mix time for [redacted]. As a result, the viscosity readings taken for the top (4140 cps) and bottom (4160 cps) for lot BL08431 were out of specifications for viscosity [redacted]

   B) The manufacturing batch record for lot # BL10731 (Hydrocortisone Spray) documented a mixing time of [redacted] minutes ([redacted]. However, batch record BL10531 (Hydrocortisone Spray) had a [redacted] minute mix time for the same step. In addition, batch record BL10731 documented a mixing time of [redacted] minutes ([redacted] for [redacted] where the batch record for lot BL10531 documented a [redacted] minute mix time for the same step.

4. Your firm failed to conduct thorough investigations that would extend to other batches of the same products that may have been associated with the specific failure or discrepancy as required by 21 CFR 211.192. For example:

   A) There was no investigation report (Standard Operating Procedure # 158-2) documented for the viscosity failures (4140cps & 4160cps with a specification of [redacted] for lot BL08431 (Hydrocortisone Shampoo). These viscosity failures resulted in a rework of the batch by adding [redacted] in order to bring lot BL08431 within specifications. There was no investigation conducted by your firm that would extend to other batches of the same products that would include conclusions and follow up.

   B) There was no documented laboratory investigation (viscosity failures of 5310cps & 5150cps with a specification of [redacted] for lot BL 33121 (Hydrocortisone Shampoo) as required by your investigational procedure 158-2, effective March 13, 2002. The action taken by your firm was to perform a rework for lot # BL33121 that included adding [redacted] which resulted in additional viscosity failures (4340cps & 3930cps). The final action taken was to make off formula changes without performing a thorough investigation that would extend to other batches of the same products that may have been associated with the specific failure or discrepancy.

   C) There were no failure investigations conducted for stability lots # BL09421 (Hydrocortisone Shampoo), BL605771 (Hydrocortisone Shampoo), and BL09121 (Hydrocortisone Spray) for the following documented batch failures: BL09421 (viscosity 720cps, spec: [redacted]); BL605771 (active ingredient, hydrocortisone 0.44, spec: [redacted] & viscosity, spec: 850cps, spec: [redacted]); and BL09121 (PH 7.8, spec: [redacted]

5. The written stability program for drug products does not describe the storage conditions for samples retained for testing as required by 21 CFR 211.166(a)(2). Specifically, the stability samples for the hydrocortisone products were stored in a room that the temperature and/or humidity conditions were not monitored or controlled. Procedure 188-0, Hydrocortisone Products Stability Testing, effective May 28, 2003 collected during the current inspection does not specify the storage conditions (temperature/humidity) for samples retained for testing.

   Furthermore, an adequate number of batches of each drug product are not tested to determine an appropriate expiration date as required by 21 CFR 211.166(b). Specifically, there was a failure to test an adequate number of stability samples for Hydrocortisone Shampoo to support a four year expiration date. For example:

   A) Lot # BL602781 was not tested for the 48-month time interval.

   B) Lot # BL605591 was not tested for the 36-month time interval.

C) Lot # BL608301 was not tested for the 24-month interval.

Your current response dated July 10, 2003 indicates that the stability tables have been updated for the above lots. However, your written response dated July 10, 2003 for FDA-483 observation 7 indicates that a new stability protocol needed to be written for the Hydrocortisone Anti-Itch Shampoo since the stability samples were stored in a room that the temperature / humidity conditions were not monitored and controlled. Your firm is responsible for establishing storage requirements for the hydrocortisone finish products and providing reliable stability data in support of a four year shelf life.

6. The written stability program for drug products does not include reliable, meaningful, and specific test methods as required by 21 CFR 211.166(a)(3). Specifically, test methods 354–(03, 02, 01, 0) and 428-0, which were used to perform stability testing for Hydrocortisone (Spray, Spot, Shampoo) products and Once-a-Month Wormer does not quantitate the amount of unknown and /or known impurities in finish drug products. There is no assurance that the above methods can detect the presence of impurities in the finish drug products referenced above.

7. Procedures describing in sufficient detail the controls employed for the issuance of labeling are not written and followed as required by 21 CFR 211.125(f). Specifically, production records for Hydrocortisone Shampoo (Lot # BL11231), Hydrocortisone Spray (Lot # BL10731), Hydrocortisone Spot (Lot # BL11431), and Once-a-month Wormer (Lot # BL09431) did not include a reconciliation of labels or preprinted packaging containers used.

8. A warning statement was not on the labeling of your Hydrocortisone products as required by 21 CFR 510.410. The lack of this statement renders your product misbranded under 502(f)(2).

This letter is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of The Act and regulations. The specific violations noted in this letter and on the Form FDA483 issued at the conclusion of the inspections may be symptomatic of serious underlying problems within your establishment's manufacturing and quality control systems. You are responsible for investigating and determining the causes of the violations identified by the FDA. Federal agencies are advised of the issuance of all Warning Letters so that they may take this information into account when considering the award of contracts.

We have received the written responses from your firm dated May 16, 2003 and July 10, 2003. In addition, we have received your written response to the FDA-483 that was issued to your firm on March 5, 2003. Your responses do not provide sufficient detail for us to evaluate whether the referenced corrective actions are adequate. For example, your response dated July 10, 2003 for observation one does not address the residual carry over of detergents in non-dedicated manufacturing equipment for your Hydrocortisone (Spray, Shampoo, Spot) products. In addition, there was no evaluation performed concerning the

acceptable level of residual carry over for your insecticides and detergents in order to prevent drug product contamination.

Your response dated July 10, 2003 for observation two indicates that your firm will not be able to validate the manufacturing process for Hydrocortisone Spray, Hydrocortisone Shampoo, and Hydrocortisone Spot until the [redacted] due to equipment upgrades, and that these products are typically only manufactured [redacted] This response to this observation is not adequate since you continue to release the Hydrocortisone (Spray, Shampoo, Spot) products commercially without a validated manufacturing process. Your firm needs to establish acceptable in-process ranges (mixing times), which will not cause variability in the characteristics of in-process material and the drug product.

Your written response dated July 10, 2003 for observation three does not evaluate the impact the failures (viscosity failures, and active ingredient stability failures) could have on other batches of the same product, which would include a corrective action plan to prevent reoccurrences of the same out of specification results for you hydrocortisone products.

Your written response dated May 16, 2003 for Hartz Once-a-Month Wormer (428-0), and your written response dated July 10, 2003 for observation five does not provide a test method to determine the amount of impurities in your drug products. In addition, has test method TM # 425-0 (Determination of Primary Amines in Piperazine Adipate Raw Material and Once-A-Month Wormer Finished Product, effective 10/6/02), provided in your July 10, 2003 been validated with respect to your new S.O.P procedure 118-1 (Validation of Test Method, effective June 2, 2003)?

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action being initiated by the FDA without further informal notice to you. These actions include, but are not limited to seizure and injunction.

Please notify this office in writing within fifteen working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to identify and make corrections to any underlying systems problems necessary to assure that similar violations will not recur. Your response should be directed to the New Jersey District, FDA, 10 Waterview Blvd., 3rd Floor, Parsippany, New Jersey 07054, Attn: Robert J. Maffei, Compliance Officer.

Sincerely,

Diana Amador-Toro for

Douglas I. Ellsworth
District Director
New Jersey District